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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/644,221	08/19/2003	Hitoshi Nagaoka	1217-031377	6470

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EXAMINER	
MARX, IRENE	
ART UNIT	PAPER NUMBER
1651	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/644,221	NAGAOKA, HITOSHI	
	Examiner	Art Unit	
	Irene Marx	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 2* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 11/30/06 is acknowledged. Claims 1-2 are being considered on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague, indefinite and confusing in lacking clear antecedent basis for "said purified, concentrated extract" at lines 1-2 of (f) or for "said extract" at line 3. The extract is characterized as "purified, concentrated pharmaceutical *Lentinus edodes* mycelium extract" under (e).

In addition, the extract is indicated as "weakens HIV activity and inhibits HIV proliferation in said human". However, the claim is at least ambiguous whether the "at least one effective dose" achieves this result. As noted previously, the recitation of "at least one effective dose" is not clearly defined in the specification, since the amount that constitutes "at least one effective dose" to be administered is not defined. There is no clear indication in the written disclosure as to the size or effectiveness intended by the dose, i.e. the intended effect of the "one effective dose" is not set forth with any particularity. In addition, the specification indicates that the mycelium extract may be administered to the infected person without dilution or by "appropriately diluting". Yet no indication is found in the as-filed specification as to what amount of the extract, whether diluted or not, it to be administered or how. In addition, the amount of dilution is not set forth with any particularity.

Response to Arguments

Applicant's arguments as they pertain to the above rejection have been fully considered but they are not deemed to be persuasive.

That Amagase administers a *Lentinus edodes* extract orally for four months and obtains favorable results against Hepatitis B is noted. However, applicant has not shown a correlation between this paper and the "at least one effective dose" of the specific extract which is not defined in the instant specification administered orally to weaken HIV activity and inhibit HIV proliferation in a human infected with HIV. See also the discussion *infra.*

While the Chen declaration indicates that the oral dose of 2 g daily was administered, the length of treatment is not revealed and there is no clear nexus between the results in the declaration pertaining to 2 g daily of an extract powder and a non-specified "at least one effective dose" administered orally to weaken HIV activity and inhibit HIV proliferation in a human infected with HIV. See also the discussion *infra.*

Therefore the rejection is deemed proper and it is adhered to.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 2 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

The claims are broadly drawn to a method of treating a human infected with HIV by orally administering at least one effective dose, without amounts and concentrations.

It is noted that the at least one effective dose is never defined or identified in the instant written disclosure nor is the intended effect of this dose clearly delineated.

Moreover, applicant intends to treat a human infected with the human immunodeficiency virus. It is well recognized that HIV infections are notoriously difficult to treat. The effect of the administration of a *Lentinus edodes* extract is not predictable for this purpose. First, there is the issue of the exact preparation utilized. Not all *Lentinus edodes* extracts are identical, i.e., possess the same or substantially the same active ingredients, even if there is a minimum content of the unknown active ingredient(s), and they are prepared in the same or substantially the same method, and thus would not work identically. The activities possessed by different fungal preparations would have different effects on different individuals, depending on their age, state of health, weight, sensitivity to allergens. Similarly, *Lentinus edodes* extracts would vary in their purity. In the instant case the size of the openings in the mesh do not appear to be indicated. In addition, Applicant does not disclose the *Lentinus edodes* strains necessary as the source of the extract.

Finally, applicants present as a single working embodiment the treatment of MT-4 cells infected with one particular strain of HIV. The data of Table 1, for example, show only inhibition of the HIV virus in MT-4 cells and not in living organisms. Thus, the in vitro "testing" done on the record fails to correlate with the treatment of a human as claimed with an "at least one effective dose".

Regarding the lack of necessary correlation between *in vitro* results and *in vivo* effects regarding the activity of an agent in the setting of HIV-infection see, e.g., Suzuki *et al.* (1989), page 372, paragraph 5. It is mentioned therein that issues such as bioavailability, metabolic features, and toxicities as well as other factors may negate the usefulness of a given agent. The fact that *Lentinus edodes* has been administered orally as a natural nutrient for a long time in Japan, does not ensure that the extract as claimed will be effective in at least one dose to achieve effective concentrations in plasma, for example, by "administering at least one effective dose... to a human afflicted with a viral disease, wherein said viral disease is human immunodeficiency virus". Another issue to be considered is the degradation and loss of antiviral effects in the

complex physiological environment of the human or animal body. Therefore, the results of the instant method of treating are unpredictable.

While a singular, narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art and the direction applicants present, provides additional weight to the lack of enablement in consideration of the *Wands* factors as a whole. Applicant's attention is also directed to Pauwels (2006) which discusses the current state of the art with respect to the discovery of effective therapeutic agents and the challenges and difficulties of producing anti-HIV drugs that are effective, due to the complex nature of the virus, its variability and tendency towards becoming resistant to various treatments or drugs. See, e.g., pages 79 et seq.

Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention. The scope of the claims is not commensurate with the teachings of enablement of the specification.

Response to Arguments

Applicant's arguments and declarations as they pertain to the above rejection have been fully considered but they are not deemed to be persuasive.

Applicant's statements regarding the interchangeability of all *Lentinus edodes* strains for the purpose of this invention are noted. However, there is no clear evidence for these unsubstantiated allegations that the unidentified used is exemplary of all *Lentinus edodes* strains.

In addition, applicant appears to rely on results pertaining to hepatitis B to attempt to overcome the deficiencies of the instant written disclosure. For example, applicant relies for a paper by Amagase to argue that the "extract is a recognized, powerful immunomodulator" and that administering at least one effective does over a long period of time is within the skill of the art. However, was is not indicated is that there is an effect on weakening of HIV activity and inhibition of HIV proliferation in a human when the extract is administered orally in at least one effective dose to an individual whose immune system has been ravaged by the effects of HIV infection..

In addition, the results of the Chen declaration pertaining to treatment of hepatitis B are cited in an attempt to extrapolate to a weakening of HIV activity and inhibition of HIV proliferation in a human when the extract is administered orally in at least one effective dose.

However, in that declaration fifty-eight patients having acute or chronic hepatitis B (HBV) were given **2 g daily of an *Lentinus edodes* mycelium extract powder** in the form of a drink. The length of the treatment is not revealed, i.e., whether it was performed for two days, 15 days, 30 days, several months or several years. In addition, it cannot be determined whether or not the powder administered is the same the extract as claimed designated, since the extract in claims 1 and 2 is not dried and is not in powder form. In addition, there is nothing in the present application to suggest that an effective dose for the treatment of a patient infected with HIV constitutes 2 g daily of an extract powder.

It is noted that the mechanisms of action of HIV and HBV are different. HIV and HBV are different types of viruses, HIV is a retrovirus, i.e., an RNA virus (a virus composed not of DNA but of RNA). Retroviruses have the enzyme reverse transcriptase to transcribe RNA (their RNA) into DNA. The retroviral DNA can then integrate into the chromosomal DNA of the host cell to be expressed there with an RNA. After initial contact and attachment of HIV to a cell of the immune system (e.g. lymphocytes, monocytes), there is a cascade of intracellular events. The endproduct of these events is the production of massive numbers of new viral particles, death of the infected cells, and ultimate devastation of the immune system. In contrast, the hepatitis B virus belongs to a family of DNA viruses called Hepadnaviridae. These viruses primarily infect liver cells.

The results of the declaration indicate that the treatment was effective and the patient's response to treatment was evaluated by measuring serum levels of GOT and GPT enzymes as well as serum levels of hepatitis B "e" (Hbe) antigens and antibodies (a known marker for hepatitis B virus infection). The relevance of these results to the method as claimed is unclear, since no correlation is proffered to equate or correlate the touted method of treating HBV with the present treatment of a human infected with HIV wherein the immune system has been ravaged due to HIV.

There is nothing in the declarations presented to show that the extract; in fact, weakens HIV activity and inhibits HIV proliferation *in vivo* in a human infected with HIV when administered orally in at least one effective dose.

Therefore the rejection is deemed proper and it is adhered to.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Irene Marx whose telephone number is (571) 272-0919. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 .

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Irene Marx
Primary Examiner
Art Unit 1651

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